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# An Overview on Formulation and Development of Nanoparticulate Matrix Tablets for Beta Blockers

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## ABSTRACT

Nanotechnologies have a more attention in recants researches. It has more advantages over other technologies. New physical technologies and properties both at the same time in sample preparation and device fabrication evoke on account of the development. There is an exponential interest in the development of novel drug delivery systems with the help of nanoparticles. Solid lipid nanoparticles are aqueous colloidal dispersion of matrix. In this matrix is made up of biodegradable lipids. Various researchers are involved in this field because of its attention in the industry. There are many methods high shear homogenization, ultrasonication, Microemulsion, Solvent emulsification and diffusion method and solvent evaporation technique, double emulsion method, film ultrsound diffusion method etc. Solid Lipid Nanoparticles has the size ranges from 1 to 1000 nm particles can use for drug delivery system. Solid Lipid Nanoparticles with Beta blocker drugs gives us a big advantage over conventional drug delivery is to improve therapeutic efficacy and sustained drug release properties while overcoming the problems like poor solubility and low oral bioavailability of beta blocker drugs. Beta blocker drugs possess some drawbacks like low bioavailability, relatively short half-life, low permeability, and adverse side effects. For effective delivery of these beta blocker drugs, drug delivery systems are used to provide an alternative strategy to administer these agents with improved bioavailability and therapeutic effects of the beta blocker.

**Keywords:** Nanoparticles, Beta blocker, Homogenization, Microemulsion.

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## INTRODUCTION

Nanotechnology is a knowledge which comes from the fields of physics, chemistry, biology, materials science and health sciences. Nanotechnology has lots of applications in almost all field of science. Nanoparticles is defined as particulate dispersions with the size range of 10-1000nm. The drug is then dissolved, entrapped and encapsulated to a Nanoparticles matrix. [1] Nanotechnology is used to improve bioavailability of certain drugs in which the difference when compared to the conventional system has been found to be very much. An in vivo study of nanoparticles was found to have increased in bioavailability. [2] Delivery of a drug molecule to specific sites is the challenge for research areas in pharmaceutical sciences. By developing colloidal delivery systems like nanoparticles, new frontiers have opened for improving drug delivery. Nanoparticles with the special characteristics like small particle size, massive surface area and the capability of adjusting by changing the surface properties have numerous advantages over other delivery forms. [3]

Nowadays a significant effort has been made to develop nanotechnology for drug delivery, because of its advantage like it offers a suitable means of delivering small molecular weight drugs. Solid lipid Nanoparticles is an alternative drug delivery system to colloidal drug delivery systems like lipid emulsions, liposomes etc. SLN combines the advantages of different colloidal carriers and also treat some of their disadvantages. SLN is uses to improve the bioavailability of drug. Tablet gives us the lowest cost approach to dosage forms. Matrix tablets is an important tool for oral release dosage forms. [4]

## MATRIX TABLETS

**Advantages of Matrix Tablets:** [5], [6]

- Easy for manufacturing

- Versatile and effective with low cost
- Made to release high molecular weight molecules
- By using conventional processes and equipment Product based on matrix design can be manufactured.
- Dose dumping and the toxic effects are reduced due to high plasma concentration.
- They give Better control of therapeutic drug concentration.
- They improve the bioavailability of some drugs.
- They increase the stability of drug by protecting them from hydrolysis or other derivative changes in the gastrointestinal tract.

**Disadvantages of the matrix tablet:** [5]

- Necessity to remove the remaining matrix after the release of drug.
- Rates of the drug release may vary with the square root of time.
- Matrix tablet lack flexibility.

**Rationale of developing matrix devices:** [5]

- To broaden the duration of action of the drug.
- To reduce the frequency of dosing.
- To reduce inter and intra subject variability.
- To minimize the fluctuations in plasma level.
- To improve drug utilization.
- To reduce adverse effects.

**Types of matrix systems:**

The matrix system can be divided into five categories depending on the types of retarding agents or polymeric materials.

**1. Hydrophobic matrix systems:**

In this matrix system the primary rate-controlling components of the hydrophobic matrix are water-insoluble in nature. Waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, Methyl Cellulose and acrylate copolymers like ingredients are used. To alter drug release, it may be necessary to incorporate soluble ingredients like lactose into the formulation. The presence of an insoluble ingredient in the formulations helps to balance the physical dimension of the hydrophobic matrix while the drug is release. The diffusion of the active ingredient is the release mechanism and corresponding release characteristic can be described by Higuchi kinetic model. Hydrophobic matrix provides programmable rates of delivery, which have become more important. Constant rate delivery has been one among the primary targets. It is used especially for a drug with narrow therapeutic index. [7]

**2. Hydrophilic matrix system:**

In this the primary rate-limiting ingredients of hydrophilic matrix are polymers that would work well when comes in contact with the aqueous solution, form a gel layer on the surface of the system. When the release medium i.e. water is compatible with a polymer then the solvent penetrates into the free spaces between macromolecular chains. Polymer may undergo a relaxation process, because of the stress of the penetrated solvent so the polymer chains become more flexible and the matrix swells. This allows the encapsulation of a drug to diffuse more rapidly out of the matrix. It would take more time to diffuse out of the matrix when the matrix swelling lengthens the diffusion path. It has been widely known for swelling and diffusion, which are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, dissolution is another important mechanism that can modulate the drug delivery rate. While swelling, dissolution can be the predominant factor for a specific type of polymers. The drug release kinetics is a combination of these two mechanisms. The increase mobility of polymeric chain gives the transport of dissolved drug. [7]

**Different factors effecting rate drug release from matrix systems**:

The release of drug from polymer matrix is dependent upon the physicochemical properties of drug and polymer and it is also dependent on several biological parameters

**1. Swelling property of polymer:**

Polymer dissolution including adsorption of water in more accessible places that rupture the polymer-polymer linking with the simultaneously form water-polymer linking, separation of polymeric chains, swelling. Finally, dispersion of polymeric chain in dissolution medium is done which indicates study of polymer hydration process for the polymers is required.[8]

**2. Drug solubility:**

Molecular size and water solubility of the drug are determinants in the release of drug which is from swelling and erosion of controlled polymeric matrices. For the drugs with reasonable aqueous solubility, the release of drugs occurs by dissolution medium and for drugs with poor solubility, release occurs by dissolution of drug particles through erosion of the matrix tablet. [9]

**3. Solubility:**

In vivo sink condition maintained actively by hem perfusion, it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. [8]

**4. Drug loading dose:**

Effect of initial drug loading of the tablets on the resulting release kinetics is more complex with poorly water soluble drugs which further increase the initial drug loading. The relative release rate first decreases and then increases where the absolute release rate increases. While the amount of drug present at a certain position in the matrix exceeds the amount of drug soluble and the excess of drug has to be considered as non-dissolved. [9]

**5. Additives:**

Effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce an increase in the release rate of hydro soluble active principles. [8]

**6. Dose size:**

In this there is an upper limit to the bulk size of the dose to be administered. Compounds which requires large dose size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in the administration of a large amount of a drug with a narrow therapeutic range. [8]

**Mechanism of Drug Release from Matrix System:**

**1) Diffusion method:**

In this method the outside layer of the drug is exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This method continues with the interface between the bathing solution and the solid drug which moves towards the interior. It follows for this system to be diffusion controlled. The rate of dissolution of drug particles in matrix must be much faster than the diffusion rate of dissolved drug while leaving the matrix. [5]

**Derivation of the mathematical model to describe this system involves following assumption:**

Pseudo steady state is maintained while the drug is releases. Drug particles have diameter less than the average distance of the drug diffusion through the matrix. Bathing solution gives us the sink condition at all times. [10]

If a system is diffusion controlled then it is expected that a plot of drug release vs. square root of time then the result will come in straight line. When the drug is release from a porous matrix it involves simultaneous penetration of surrounding liquid, dissolution and leaching of the drug through winding interstitial channels. The volume and length of the openings must be noted for the drug release from a porous or granular matrix: [5]

$$M = \left[ {}^{D_s . C_a . p}\!/\!_{T.(2C_0 - p.C_a).t} \right]^{1/2}$$

Where, p is Porosity of the matrix,

t is Tortuosity,

$C_a$ is solubility of the drug in the release medium,

$D_s$ is Diffusion coefficient in the release medium and

T is Diffusional path length.

For pseudo steady state, the equation can be written as:

$$M = \left[ 2D . C_a . C_o ({}^{p}\!/\!_{T}) . t \right]^{1/2}$$

The total porosity of the matrix can be calculated with the following equation:

$$p = pa + C_a/\rho + C_{ex}/\rho_{ex}$$

Where, p is Porosity,

ρ is Drug density,

$P_a$ is Porosity due to air pockets in the matrix,

$\rho_{ex}$ is Density of the water soluble excipients and

$C_{ex}$ is Concentration of water soluble excipient. [5]

**Higuchi model:**

The drug release from Higuchi model is slower than zero order profile. When a matrix tablet is placed in the dissolution medium the initial release occurs from the tablet superficial layer and the release rate is fast. When time passes the external layers of the tablet become depleted of the drug and water molecule must travel through long channels to reach the drug which remains into the tablet. [10] Similarly when the drug solution is formed in the tablet, it must diffuse through long capillaries to reach the external dissolution medium. The reason for continuous decrease in rate of the drug release is more than for the matrix swells. When the longer is the diffusion path length then it requires for the drug to come out longer. [5]

$$Q = k.t.n$$

Where, Q is Fraction of drug release in time (t),

t is Time,

k is Rate constant (incorporates characteristics of polymer system and drug) and

n is Diffusional exponent [5]

## CLASSIFICATION OF MATRIX TABLET

**1. Hydrophobic matrices:**

The concept of using hydrophobic material as matrix tablet was first introduced in 1959. This method is very popular as in this method to obtain an oral dosage form, then the drug is mixed with a hydrophobic polymer and at that time then it compressed to a tablet. Drug released is obtained because the dissolving drug is diffused through channels which exist between compacted polymer particles. Hydrophobic matrices are the only system into which the use of polymer isn't essential for providing drug release, when insoluble polymers have been used. Primary rate controlling component of hydrophobic matrix are water insoluble in nature like waxes, glycerides and polymeric materials such as methyl cellulose, ethyl cellulose to modulate the release rate of drug. [11]

**2. Lipid matrices:**

These matrices were prepared by lipid waxes and related materials. Drug release from such material occurs through pore diffusion and erosion. Release characteristic are then more sensitive to digestive fluid composition than to totally insoluble polymer matrix. [12]

**3. Hydrophilic matrix tablets:**

Hydrophilic matrix is presently one of the most interesting drug delivery systems which are most widely used to control the release rate of drugs with their flexibility to obtain desirable both drug release profile and broad regulatory acceptance. It defined as a Homogeneous dispersion of drug molecules within a skeleton of hydrophilic polymers which can swells upon contact with water. These systems are known as swellable-controlled release systems. When the release rate is observed it can be the zero-order release. Most hydrophilic matrices are obtained by compression. [13]

**4. Biodegradable Matrices:**

These consist of the polymers which then comprised of monomers linked to each other by functional groups which further have unstable linkage in the backbone. It is degraded by enzymes which are generated by surrounding living cells in oligomers that can be metabolized or excreted. Examples are natural polymers like proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly and poly anhydrides.[13]

**5. Mineral Matrices:**

These include polymers which are obtained from various species of seaweeds. Example: Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds by the use of dilute alkali.[5],[13]

## NANOPARTICULATE DRUG DELIVERY

**Rationale for using Nanoparticles for oral drug delivery:**

Drug with low aqueous solubility and low permeability (i.e. BCS class II, III, IV drugs) are difficult to deliver by oral route. The difficulty arises due to varying GI pH and low bioavailability. [14]

This wide difference in the pH can severely hamper the pharmacological activity of the drug Oral bioavailability of some is affected as they undergo chemical degradation at acidic pH. Different liver Enzymes cause significant degradation of antihypertensive drugs Intestinal mucosa is the other barrier which cause obstacle to drug permeation. Gastric mucosal barrier includes extrinsic barrier and intrinsic barrier. Tight junction between two cells make intrinsic barrier. There are different mechanisms by which any molecule can cross the barrier viz. transcytosis, paracellular and transcellular. Being an active transport pathway, transcytosis restricts charged molecules and molecules with large size. [15]

Mucoadhesive formulations can be formulated to overcome the intestinal barrier so to increase time of contact with mucus and increases the drug concentration at the site of drug absorption. Some mucoadhesive agents have the property of enhancing the permeation by Paracellular occurs due to opening the tight junction. Another approach to enhance GI permeability is by carrying out transport of drug molecule through M cells possessing lesser quantity of protease enzyme and also lacks mucus secretion. [16]

Solid Lipid nanoparticles (SLN) and Nanostructured lipid carriers (NLC) can be transferred by clathrin-mediated transport through intestinal barrier. Solid Lipid nanoparticles can be transferred using trnscytosisis by caveolae-mediated endocytosis and Nanostructured lipid carriers can be transported through tight junctions of cells by means of paracellular transport [17]

Nanoparticulate systems like nanoemulsion, liposome, Solid Lipid nanoparticles and Nanostructured lipid carriers have been found to surpass first-pass metabolism by means of lymphatic transport. Charge present on the nanoparticles affects Lymphatic update and hence negatively charged particles exhibits higher lymphatic uptake. [18] Efflux transporter such as P-glycoprotein located on the intestinal wall promotes efflux of some of antihypertensive causing poor oral bioavailability of these drugs. [19] Such difficulties can be avoided and along with this, sustained release for dose and administration frequency reduction can be achieved by encapsulating drug in nanoparticles. [20]

## A. SOLID LIPID NANOPARTICLES

**Aim for preparation of Solid lipid nanoparticles:**

- Increased drug stability.
- High drug pay load.
- No toxicity of carrier.
- Avoidance of organic solvents.
- Incorporation of lipophilic and hydrophilic drug matrix. [21]

**Method for preparation of solid lipid Nanoparticles:**

**1. High pressure homogenization:**

It pushes the liquid down with high pressure at hollow gap of some few microns which are nearly 100Km/h rate and with high viscosity the fluid accelerates to a very short distance. Very high-pressure stress force interrupts the particle down to submicron size range with 5-40% lipid content. There are two homogenization methods (A) hot homogenization (B) Cold homogenization method which are used for the production of SLN. [21]

**a) Hot homogenization:**

This is an emulsion which can be carried out in above the melting point of the liquid. With this of high share mixing device, a pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase is obtained has a same temperature. The HPH of pre emulsion can be carried out on the above liquid melting point. Because of the decrease viscosity of inner phase of emulsion in high temperature, particle size would be lower. With the Increase in the homogenization pressure or the number of cycles increases the particle size due to high kinetic energy of the particles. [21]

**b) Cold homogenization:**

This has been developing to over-come the temperature related degradation problems, loss of drug in the aqueous phase and partitioning associated with hot homogenization method. Due to complexity of the crystallization step of the nano emulsion resulting in several modifications and super cooled melts, leads to Unpredictable polymeric transitions of the lipid. Here, drug is incorporated in melted lipid and the lipid melt is cooled rapidly using dry ice or liquid nitrogen. The solid material is ground by a mortar mill. The prepared lipid nanoparticles and micro particles are then dispersed in a cold emulsifier solution at or below room temperature. The temperature should be regulated to ensure solid state of the lipid during homogenization. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenization sample. [21]

**Advantages:**

- It has a Low capital cost.
- It demonstrated at lab scale. [22]

**Disadvantages:**

- Energy intensive process.
- Poly disperses distributions. [22]

**2. Solvent Evaporation method:**

In this method drug which is lipophilic in nature is dissolved into a water-immiscible organic solvent and it is then emulsified in an aqueous phase which contains the surfactant under continuous stirring of magnetic stirrer. The organic solvent was then evaporated and nanoparticulate dispersion is formed by precipitation of the lipid. [21]

**Advantages:**

- It is Scalable.
- It has mature technology.
- It is a continuous process.
- It commercially demonstrated. [22]

**Disadvantages:**

- It is extremely energy intensive process.
- It has poly disperses distributions.
- It causes bimolecular damage.[22]

### 3. Micro emulsion-based method:

This method is based on dilution of microemulsions. Microemulsions are two-phase systems made up of an inner and outer phase. They are made by stirring an optically transparent mixture, which typically composed of a low melting fatty acid. The hot microemulsion is then dispersed in cold water (2-3°C) with stirring. This dispersion can be used in this process as granulation fluid for transferring in to solid product (tablets, pellets) by granulation process but when in case of low particle content too much of water needs to be removed. High-temperature facilitates rapid lipid crystallization and it also prevents aggregation, because of the dilution step achievable lipid contents are lower compared with HPH based formulations. [21]

**Advantages:**

- It has a low mechanical energy input.
- It has a theoretical stability. [22]

**Disadvantages:**

- It is extremely sensitive to change.
- Labor intensive formulation work.
- It has a low nanoparticles concentration.[22]

### 4. Solvent emulsification method:

In this technique, the solvent used are must be partially miscible with water. This technique is carried out either in aqueous phase or in oil phase. Both the solvent and water were mutually saturated in order to ensure the initial thermodynamic equilibrium of liquid. When heating is required to solubilize the lipid, then saturation step was performed at that temperature. Then the lipid and drug were dissolved in water saturated solvent and this organic phase was emulsified with solvent saturated solution containing stabilizer using mechanical stirrer. After the formation, water in typical ratio ranges from 1:5 to 1:10, were added to the system in order to allow solvent diffusion into the continuous phase, thus forming aggregation of the lipid in the nanoparticles. Here the phases were maintained at same elevated temperature and the diffusion step was performed either at room temperature or at the temperature, in which it is the lipid was dissolved. Throughout the process constant stirring was maintained. Lastly, the diffused solvent was eliminated by vacuum distillation.[21]

### 5. Double Emulsion method:

In double emulsion method a drug is encapsulated with stabilizer initially, which prevent the partitioning of drug in external water phase while solvent evaporation in the external water phase of double emulsion. [22]

### 6. Film ultrasound dispersion:

In this method the lipid and drug were put in suitable organic solution and after decompression, rotation and evaporation then lipid is formed. Then the solution including the emulsion was added. With the help of the ultrasound with the probe of diffuser, SLN with little and uniform particle size is formed.[22]

**Advantages of SLN:**

- The main Use of biodegradable physiological lipid matrix. It decreases the danger of acute and chronic toxicity production methods.[23]
- It Improved bioavailability of poorly water soluble drugs.
- It gives Target specific delivery of drugs which further enhanced drug penetration into the skin
- It gives Protection to chemically labile agents from degradation and sensitive drugs from outer environment.
- SLNs have better stability compared to liposomes
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated com-pound. [4]
- High concentration of compound.
- Easy scale up is possible of solid lipid Nanoparticles. It gives good stability.[5]

**Disadvantages of SLN:**

- It has Poor drug loading capacity,[2, 3]
- Drug expulsion after polymeric transition during storage
- Relatively high water content of the dispersions [3]
- It has some uncertain gelation tendency. [5]
- Some of uneven kinetics for polymeric transition.
- It shows some particle growth during storage.
- Relatively higher water content of the dispersion.[5]

**Applications (For beta blockers delivery):**

- SLN for beta blockers are used to improve therapeutic efficacy and sustained drug release properties which overcomes the problems such as poor solubility and low oral bioavailability.[24]
- SLN for beta blockers is also used to prevent high first-pass metabolism.[22]
- SLN for beta blockers are used to enhance onset of action of a drug.[24]
- Beta blockers provides a promising approach for enhancing solubility.[22]
- SLN for beta blockers are used to avoid chlorinated solvents, surfactants to minimize their toxic effects.[25]
- Beta blockers are useful when combining multiple classes of antihypertensive drugs together that is one of the most important factors for achieving blood pressure control[26]
- Most commonly SLN for beta blockers are also used to treat hypertension because β-blockers are potent and highly effective.[26]
- Beta blockers are the quantum of their utilization to overcome this problem beta blocker is formed with SLN.
- Beta blockers overloaded with nanoparticles are also used in ocular drug delivery. [27]

e.g. Venishetty VK (2012): [28] prepared carvedilol loaded Solid lipid nanoparticles coated with N-carboxymethyl chitosan. The main aim behind coating of SLN was to protect drug from releasing rapidly in acidic environment. For the preparation of SLN monoglycerides was used as lipid, and surfactant used was lecithin and charged modifier used was

stearylamine. Prepared uncoated SLN were then subjected to different evaluation parameters like crystallinity, determination of particle size, determination of zeta potential and entrapment efficacy and stability studies. After that coated SLN were characterized by zeta potential and analysis X-ray by Photon Spectroscopy. Drug release studies were carried out IN-vitro and in rats. Coating imparts enhanced bioavailability of carvedilol as compared to uncoated one.

### B. NANOSUSPENSIONS [29]

Nanosuspension can be defined as colloidal dispersions of drug particles biphasic in nature and stabilized with the help of surfactants. Particle size of dispersed phase is less than 1 µm. Poorly water soluble drugs can be delivered due to nano size. Solid content of nanosuspension can be increased up to 40% so to reduce the size of dose and so to improve patient compliance nanosuspension can be converted into dosage forms. Like pellets or tablets, with the use of different methods like extrusion-spheronization and spray/ freeze drying.

e.g. Thadkala et al. (2015) [30]: developed oral nanosuspension tablet of Nebivolol HCl for the improvement of dissolution rate and so the absorption. Nebivolol hydrochloride belongs to BCS Class II and is lipophilic in nature. Nebivolol nanosuspension was formulated using solvent displacement method. Optimized formulation showed maximum drug release than pure drug and followed first order release kinetics.

### C. DENDRIMERS[9]

Dendrimers can be defined as highly branched polymeric carrier which are star-shaped macromolecules with dimensions in nanometers(1-100nm) Dendrimers have unique properties like narrow polydispersity index with controlled molecular structure and 3D structure. These are multivalent entity with multiple functional groups. Dendrimers consist of three domains –a core, branches and terminally attached functional group. Polymers used in dendrimers are polyamines, polyamidoamines, polyamides (polypeptides) and poly (aryl ethers). Most commonly used dendrimers are polyamidoamines. Different genes, peptides and proteins can be delivered using Dendrimers. Also, they can be used for Immunoassay, gene therapy and solubilization purpose. Different antihypertensive drugs can be delivered by oral route successfully by conjugation and encapsulation within dendrimers which bypasses efflux transporter. Solubility improvement depends upon different factors like pH and concentration of dendrimers and, size of generation, temperature, core and terminal functionality . D'Emanuele A., et al., (2004): [31] carried out a study with the aim of solubility improvement of Propranolol. Propranolol was conjugated with lauroyl-G3. The formulated drug-dendrimers conjugates showed enhanced solubility as compared to pure drug

### D. PROLIPOSOMES [29]

Proliposomes are dry and free-flowing particles having a dispersed system. This dispersed system can be immediately converted into liposomal suspensions when come in contact with aqueous phase. Proliposomes are more advantageous in terms of drug absorption when compared with conventional liposomes. Solid properties of proliposomes make them physically more stable without any change in intrinsic properties, helps to improve solubility of different hydrophobic drugs. Kim et al. (2008): [32] developed proliposomes formulation for Propranolol for achieving sustained drug release Formulated proliposomes showed good micromeritics and flow properties.

## CONCLUSION

Nanotechnology has a great potential for effective delivery of poorly soluble drugs with improving solubility and oral bioavailability. Most of the beta blockers can be delivered successfully at the site of absorption by using novel drug delivery systems with the incorporation of nanoparticles. Novel drug delivery system possesses numerous benefits in terms of improved bioavailability and so the therapeutic efficacy and improved targeting. Different NDDS with Nanoparticulate systems like solid lipid nanoparticles, dendrimers, nano-suspensions and proliposomes can be formulated into matrix tablets for successful delivery of beta blockers at site of absorption.SLN can enhance production scalability and improved drug targeting, while nanosuspension can improve water solubility of β blockers with their nano size. Multivalent and highly branched Dendrimers provide ease of binding, while proliposomes provide improved flow characteristics for beta blockers. Therefore, Matrix tablets of β-blockers with Nanoparticulate system can be successfully formulated.

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## CONFLICT OF INTEREST

The authors declared that they have no any conflict of interest.

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